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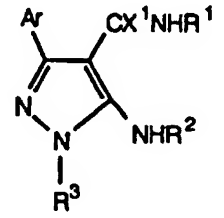
(57) Abstract



(1)

Compounds of general formula (1) are described, wherein Ar is an optionally substituted aromatic or heteroaromatic group; X^1 is an oxygen or sulphur atom; R^1 is a hydrogen atom or a methyl group; R^2 is a hydrogen atom or a group $-Alk^1$ or $-X^2Alk^1$ where Alk^1 is an optionally substituted aliphatic or heteroaliphatic group and X^2 is a -C(O)-, -C(S)-, or $-S(O)_n$ group where n is an integer 1 or 2; R^3 is a hydrogen atom or a group $-Alk^2$, [where Alk^2 is as defined for Alk^1], $-X^2Alk^2$, $-Ar^1$ [where Ar^1 is an optionally substituted aromatic or heteroaromatic group], $-Alk^2Ar^1$, or $-X^2Alk^2Ar^1$; and the salts, solvates, hydrates and N-oxides thereof. The compounds are selective inhibitors of the protein tyrosine kinase $p56^{lck}$ and are of use in the prophylaxis and treatement of immune diseases, hyperproliferative disorders and other diseases in which inappropriate $p56^{lck}$ activity is believed to have a role.

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5-AMINOPYRAZOLES USEFUL AS SELECTIVE INHIBITORS OF THE PROTEIN TYROSINE KINASE P56ICK

This invention relates to a series of substituted pyrazoles, to processes for their preparation, to pharmaceutical compositions containing them, and to their use in medicine.

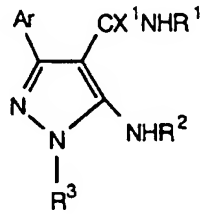
Protein kinases participate in the signalling events which control the activation, growth and differentiation of cells in response to extracellular mediators and to changes in the environment. In general, these kinases fall into two groups; those which preferentially phosphorylate serine and/or threonine residues and those which preferentially phosphorylate tyrosine residues [Hanks, S K, Hunter T, FASEB. J. 9, 576-596 (1995)]. The serine/threonine kinases include for example, protein kinase C isoforms [Newton A C, J. Biol. Chem. 270, 28495-28498 (1995)] and a group of cyclin-dependent kinases such as cdc2 [Pines J, Trends in Biochemical Sciences 18, 195-197 (1995)]. The tyrosine kinases include membrane-spanning growth factor receptors such as the epidermal growth factor receptor [Iwashita S and Kobayashi M. Cellular Signalling 4, 123-132 (1992)], and cytosolic non-receptor kinases such as $p56^{lck}$, $p59^{fyn}$, ZAP-70 and csk kinases [Chan C *et al* Ann. Rev. Immunol. 12, 555-592 (1994)].

Inappropriately high protein kinase activity has been implicated in many diseases resulting from abnormal cellular function. This might arise either directly or indirectly, for example by failure of the proper control mechanisms for the kinase, related for example to mutation, overexpression or inappropriate activation of the enzyme; or by over- or underproduction of cytokines or growth factors also participating in the transduction of signal upstream or downstream of the kinase. In all of these instances, selective inhibition of the action of the kinase might be expected to have a beneficial effect.

We have now found a series of 5-aminopyrazole derivatives which are potent and selective inhibitors of the protein tyrosine kinase $p56^{lck}$. The compounds are of use in the prophylaxis and treatment of immune

diseases, hyperproliferative disorders and other diseases in which inappropriate $p56^{lck}$ activity is believed to have a role.

Thus according to one aspect of the invention, we provide a compound of formula (1):



(1)

wherein

Ar is an optionally substituted aromatic or heteroaromatic group;

X^1 is an oxygen or sulphur atom;

R^1 is a hydrogen atom or a methyl group;

R^2 is a hydrogen atom or a group $-Alk^1$ or $-X^2Alk^1$ where Alk^1 is an optionally substituted aliphatic or heteroaliphatic group and X^2 is a -C(O)-, -C(S)-, or $-S(O)_n$ group where n is an integer 1 or 2;

R^3 is a hydrogen atom or a group $-Alk^2$, [where Alk^2 is as defined for Alk^1], $-X^2Alk^2$, $-Ar^1$ [where Ar^1 is an optionally substituted aromatic or heteroaromatic group], $-Alk^2Ar^1$, or $-X^2Alk^2Ar^1$;

and the salts, solvates, hydrates and N-oxides thereof.

Aromatic groups represented by the groups Ar or, when present, Ar^1 in compounds of formula (1) include for example mono- or bicyclic C_{6-12} optionally substituted aromatic groups, for example optionally substituted phenyl, 1– or 2–naphthyl, 1- or 2-tetrahydronaphthyl, indanyl or indenyl groups.

Heteroaromatic groups represented by Ar or Ar^1 include for example C_{1-9} optionally substituted heteroaromatic groups containing for example one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, the heteroaromatic groups may be for example

monocyclic or bicyclic heteroaromatic groups. Monocyclic heteroaromatic groups include for example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Bicyclic heteroaromatic groups include for example nine- to thirteen-membered heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Particular examples of heteroaromatic groups represented by Ar or Ar^1 include optionally substituted pyrrolyl, furyl, thienyl, imidazolyl, N-methylimidazolyl, N-ethylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazole, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl, isobenzothienyl, indolyl, isoindolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, quinazolinyl, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolinyl, isoquinolinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, or imidyl, e.g. succinimidyl, phthalimidyl, or naphthalimidyl such as 1,8-naphthalimidyl.

Optional substituents which may be present on the aromatic or heteroaromatic groups represented by Ar or Ar^1 include one, two, three or more groups, each represented by the group R^4. The substituent R^4 may be selected from an atom or group R^5 or $-Alk^3(R^5)_m$, where R^5 is a halogen atom, or an amino ($-NH_2$), substituted amino, nitro, cyano, hydroxyl (-OH), substituted hydroxyl, formyl, carboxyl ($-CO_2H$), esterified carboxyl, thiol (-SH), substituted thiol, $-COR^6$ [where R^6 is an $-Alk^3(R^5)_m$, aryl or heteroaryl group], $-CSR^6$, $-SO_3H$, $-SO_2R^6$ $-SO_2NH_2$, $-SO_2NHR^6$, $SO_2N[R^6]_2$, $-CONH_2$, $-CSNH_2$, $-CONHR^6$, $-CSNHR^6$, $-CON[R^6]_2$, $-CSN[R^6)_2$, $-NHSO_2H$, $-NHSO_2R^6$, $-N[SO_2R^6]_2$, $-NHSO_2NH_2$, $-NHSO_2NHR^6$, $-NHSO_2N[R^6]_2$, $-NHCOR^6$, $-NHCSR^6$, $-NHC(O)OR^6$, aryl or heteroaryl group; Alk^3 is a straight or branched C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene chain, optionally interrupted by one, two or three -O- or -S- atoms or $-S(O)_n$ or $-N(R^7)$- groups [where R^7 is a

hydrogen atom or C_{1-6}alkyl, e.g. methyl or ethyl group]; and m is zero or an integer 1, 2 or 3.

When in the group $-Alk^3(R^5)_m$ m is an integer 1, 2 or 3, it is to be understood that the substituent or substituents R^5 may be present on any suitable carbon atom in $-Alk^3$. Where more than one R^5 substituent is present these may be the same or different and may be present on the same or different atom in $-Alk^3$. Clearly, when m is zero and no substituent R^5 is present the alkylene, alkenylene or alkynylene chain represented by Alk^3 becomes an alkyl, alkenyl or alkynyl group.

When R^5 is a substituted amino group it may be for example a group $-NHR^6$ [where R^6 is as defined above] or a group $-N[R^6]_2$ wherein each R^6 group is the same or different.

When R^5 is a halogen atom it may be for example a fluorine, chlorine, bromine, or iodine atom.

When R^5 is a substituted hydroxyl or substituted thiol group it may be for example a group $-OR^6$ or a $-SR^6$ or $-SC(NH_2+)NH_2$ group respectively.

Esterified carboxyl groups represented by the group R^5 include groups of formula $-CO_2Alk^4$ wherein Alk^4 is a straight or branched, optionally substituted C_{1-8}alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; a $C_{6-12}arylC_{1-8}$alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a C_{6-12}aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a $C_{6-12}aryloxyC_{1-8}$alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyl-oxymethyl, or 2-naphthyloxymethyl group; an optionally substituted $C_{1-8}alkanoyloxyC_{1-8}$alkyl group, such as a pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; or a $C_{6-12}aroyloxyC_{1-8}$alkyl group such as an optionally substituted benzoyloxyethyl or benzoyloxypropyl group. Optional substituents present on the Alk^4 group include R^5 substituents described above.

When Alk^3 is present in or as a substituent R^4 it may be for example a methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene, s-butylene, t-butylene, ethenylene, 2-propenylene, 2-butenylene, 3-butenylene, ethynylene, 2-propynylene, 2-butynylene or 3-butynylene chain, optionally interrupred by one, two, or three -O- or -S-, atoms or -S(O)-, $-S(O)_2-$ or $-N(R^7)-$ groups.

Aryl or heteroaryl groups represented by the groups R^5 or R^6 include mono- or bicyclic optionally substituted C_{6-12} aromatic or C_{1-9} heteroaromatic groups as described above for the groups Ar and Ar^1. The aromatic and heteroaromatic groups may be attached to the remainder of the compound of formula (1) by any carbon or hetero e.g. nitrogen atom as appropriate.

Particularly useful atoms or groups represented by R^4 include fluorine, chlorine, bromine or iodine atoms, or C_{1-6}alkyl, e.g. methyl or ethyl, C_{1-6}alkylamino, e.g. methylamino or ethylamino, C_{1-6}hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, C_{1-6}alkylthiol e.g. methylthiol or ethylthiol, C_{1-6}alkoxy, e.g. methoxy or ethoxy, C_{5-7}cycloalkoxy, e.g. cyclopentyloxy, haloC_{1-6}alkyl, e.g. trifluoromethyl, haloC_{1-6}alkoxy, e.g. trifluoromethoxy, C_{1-6}alkylamino, e.g. methylamino or ethylamino, amino ($-NH_2$), aminoC_{1-6} alkyl, e.g. aminomethyl or aminoethyl, C_{1-6}dialkylamino, e.g. dimethylamino or diethylamino, imido, such as phthalimido or naphthalimido, e.g. 1,8-naphthalimido, 1,1,3-trioxobenzo-[d]thiazolidino, nitro, cyano, hydroxyl (-OH), formyl [HC(O)-], carboxyl ($-CO_2H$), $-CO_2Alk^4$ [where Alk^4 is as defined above], C_{1-6} alkanoyl e.g. acetyl, thiol (-SH), thioC_{1-6}alkyl, e.g. thiomethyl or thioethyl, $-SC(NH_2+)NH_2$, sulphonyl ($-SO_3H$), C_{1-6}alkyl-sulphonyl, e.g. methylsulphonyl, aminosulphonyl ($-SO_2NH_2$), C_{1-6}alkyl-aminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C_{1-6} dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylamino-sulphonyl, phenylamino-sulphonyl, carboxamido ($-CONH_2$), optionally substituted C_{1-6}alkylaminocarbonyl, e.g. methylaminocarbonyl, ethyl-aminocarbonyl, propylaminocarbonyl, 2-aminoethylaminocarbonyl, aminopropylaminocarbonyl, N-(methoxycarbonyl)-2-amino-carbonyl, N-(methoxycarbonyl)-3-aminopropylaminocarbonyl, N-(butoxycarbonyl)-3-aminopropylaminocarbonyl, C_{1-6} dialkylaminocarbonyl, e.g. dimethylamino-

carbonyl or diethylaminocarbonyl, sulphonylamino (-$NHSO_2H$), C_{1-6}alkyl-sulphonylamino, e.g. methylsulphonylamino or ethyl-sulphonylamino, C_{1-6} dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonyl-amino, optionally substituted phenylsulphonylamino, e.g. 2-, 3- or 4-substituted phenylsulphonylamino such as 2-nitrophenylsulphonylamino, aminosulphonylamino (-$NHSO_2NH_2$), C_{1-6}alkylamino-sulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C_{1-6}dialkyl-aminosulphonylamino, e.g. dimethylamino-sulphonylamino or diethyl-aminosulphonylamino, phenylaminosulphonyl-amino, C_{1-6}alkanoylamino, e.g. acetylamino, C_{1-6}alkanoylaminoC_{1-6}alkyl, e.g. acetylaminomethyl, or C_{1-6}alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonyl-amino or t-butoxycarbonylamino groups.

Where desired, two R^4 substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C_{2-6}alkylenedioxy group such as ethylenedioxy.

It will be appreciated that where two or more R^4 substituents are present, these need not necessarily be the same atoms and/or groups.

When the group -Alk^1 or -Alk^2 is present in the compounds of formula (1) it may be for example an optionally substituted C_{1-10}aliphatic or C_{1-10} heteroaliphatic group.

Particular examples of aliphatic groups represented by -Alk^1 or -Alk^2 include optionally substituted straight or branched C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl groups. Particular heteroaliphatic groups include the aliphatic groups just recited but each additionally containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Thus, for example, -Alk^1 or -Alk^2 when present in compounds of formula (1) may be an optionally substituted -CH_3, -CH_2CH_3, -$(CH_2)_2CH_3$, -$CH(CH_3)_2$, -$(CH_2)_3CH_3$, -$CH(CH_3)CH_2CH_3$, -$CH_2CH(CH_3)_2$, -$C(CH_3)_3$, -$(CH_2)_4CH_3$, -$(CH_2)_5CH_3$, -$CHCH_2$, -$CHCHCH_3$, -CH_2CHCH_2, -$CHCHCH_2CH_3$, -$CH_2CHCHCH_3$, -$(CH_2)_2CHCH_2$, -$CHCH(CH_2)_2CH_3$, -$CH_2CHCHCH_2CH_2$, -$(CH_2)_2CHCHCH_3$, -$(CH_2)_3CHCH_2$,

$-CHCH(CH_2)_3CH_3$, $-CH_2\ CHCH(CH_2)_2CH_3$, $-(CH_2)_2CHCHCH_2CH_3$, $-(CH_2)_3CHCHCH_3$, or $-(CH_2)_4CH_2CH_2$ group, each of said groups, where appropriate, being optionally interrupted by one or two -O- or -S- atoms and/or -C(O)-, -C(S)-, -S(O)-, $-S(O)_2-$, $-N(R^7)-$, $-CON(R^7)-$, $-OC(O)N(R^7)-$, $-CSN(R^7)-$, $-N(R^7)CO$, $-N(R^7)C(O)O-$, $-N(R^7)CS-$, $-SON(R^7)-$, $-SO_2N(R^7)-$, $-N(R^7)SO_2-$, $-N(R^7)CON(R^7)-$, $-N(R^7)CSN(R^7)-$, $-N(R^7)SON(R^7)-$ or $-N(R^7)SO_2N(R^7)-$ groups.

Optional substituents which may be present on $-Alk^1$ or $-Alk^2$ in compounds of formula (1) include one, two, three or more R^8 substituents, where R^8 is as defined above for the substituent R^4.

The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and organic bases.

Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or isethionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or napsylates, phosphates, sulphates, hydrogen sulphates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

Particularly useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

It will be appreciated that depending on the nature of the substituents R^1, R^2, R^3, R^4 and R^5 the compounds of formula (1) may exist as geometrical

isomers and/or may have one or more chiral centres so that enantiomers or diasteromers may exist. It is to be understood that the invention extends to all such isomers of the compounds of formula (1), and to mixtures thereof, including racemates.

In general in compounds of formula (1) the group R^1 is preferably a hydrogen atom.

X^1 in compounds of formula (1) is preferably an oxygen atom.

In another general preference, the group R^2 in compounds of formula (1) is preferably a hydrogen atom.

One particularly useful group of compounds according to the invention is that wherein Ar is an optionally substituted aromatic group, especially an optionally substituted phenyl or naphthyl group. In compounds of this type Ar may be in particular a phenyl group or a phenyl group substituted by one, two, three or more R^4 groups as defined herein. Especially useful Ar groups include phenyl or monosubstituted phenyl groups where the substituent is a R^4 group as defined herein. Particularly useful R^4 substituents in groups of this type include halogen atoms and optionally substituted C_{1-6}alkyl groups, especially a chlorine atom or a methyl group.

In a further preference, the group R^3 in compounds of formula (1) is an $-Alk^2$, $-X^3Alk^2$, $-Ar^1$, $-Alk^2Ar$,or $-X^3Alk^2Ar^1$ group. Particularly useful compounds of this type are those wherein R^3 is an $-Alk^2$ or Ar^1 group. Especially useful R^3 groups include optionally substituted C_{1-6}alkyl, optionally substituted phenyl or optionally substituted pyridyl groups. Particular groups of this type include t-butyl, phenyl or 2-pyridyl groups, each of said phenyl or pyridyl groups being optionally substituted by a group R^4. Particularly useful R^4 groups include halogen atoms or amino ($-NH_2$), nitro, methyl, ethyl, methoxy or ethoxy groups.

Compounds according to the invention are potent and selective inhibitors of the protein tyrosine kinase $p56^{lck}$. In particular, compounds of the invention inhibit the $p56^{lck}$ enzyme at concentrations at which they have

little or no useful inhibitory action on other protein kinases, in particular ZAP-70, protein kinase C and Csk kinases. The ability of the compounds to act in this way may be simply determined by the tests described in the Examples hereinafter.

The compounds according to the invention are thus of particular use in the prophylaxis and treatment of diseases or disorders in mammals, especially humans, in which inappropriate protein tyrosine kinase action plays a role, and the invention extends to such a use. Particular examples of diseases and disorders in which inappropriate tyrosine kinase action plays a role include autoimmune diseases such as rheumatoid arthritis, multiple sclerosis and systemic lupus erythematosus, in transplant rejection, in graft v host disease, in hyperproliferative disorders such as tumours and psoriasis, and in diseases in which cells receive pro-inflammatory signals such as asthma, inflammatory bowel disease and pancreatitis.

For use as just described the compounds according to the invention may be administered as pharmaceutical compositions containing an amount of the compound effective in the prophylaxis or treatment of the disease or disorder. Thus according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration, or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets

may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds for formula (1) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

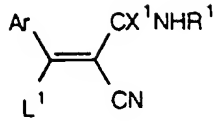
For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

The therapeutically effective amount of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however, daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. In the following process description, the symbols Ar, X^1, R^1, R^2, and R^3, when used in the formulae depicted are to be understood to represent those groups described above in relation to formula (1) unless otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, 1981]. In some instances, deprotection may be the final step in the synthesis of a compound of formula (1) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups.

Thus according to a further aspect of the invention, a compound of formula (1) wherein R^1 and R^2 is each a hydrogen atom may be prepared by reaction of an alkene of formula (2):



(2)

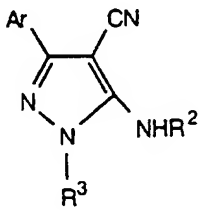
[wherein L^1 is an electron-donating leaving group], with a hydrazine R^3NHNH_2 or a salt thereof.

Particular examples of groups represented by L^1 include -OR, $-OSO_2R$, -SR and $-N(R)_2$ groups [where R is an aliphatic or heteroaliphatic group, as described herein for the group Alk^1 and may be for example an optionally substituted C_{1-6}alkyl group, such as a methyl or trifluoromethyl group].

The reaction may be performed in the presence of an organic solvent, for example an alcohol such as methanol or ethanol, or an ether, e.g. a cyclic ether such as tetrahydrofuran at an elevated temperature e.g. the reflux temperature, optionally in the presence of a base, e.g. an inorganic base such as an alkali metal base, e.g. sodium hydroxide or sodium carbonate.

Alkenes of formula (2) and hydrazines of formula R^3NHNH_2 are either known, [see for example Tominaga, Y, *et al*, J. Het. Chem., 27, 647-660, (1990)] and in some instances commercially available compounds, or may be obtained from known starting materials by methods analogous to those used for the preparation of the known compounds.

In another process according to the invention, a compound of formula (1) wherein X^1 is an oxygen atom and R^1 is a hydrogen atom may be prepared by heating a nitrile of formula (3):

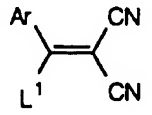


(3)

optionally either in the presence of a base, for example an inorganic base such as an alkali metal base, e.g. sodium hydroxide, in a solvent, for example an alcohol such as ethanol, or in the presence of a catalyst, for example a complex metal catalyst such as a palladium or ruthenium catalyst, e.g. tetrakis(triphenylphosphine)ruthenium dihydride in an inert organic solvent such as an ether, e.g. dimethoxyethane or dioxane or an aromatic hydrocarbon such as toluene or benzene.

The reaction may be performed at any suitable elevated temperature up to and above the reflux temperature depending on the nature of the reactants and solvents used.

Nitriles of formula (3) wherein R^2 is a hydrogen atom may be prepared by reaction of a dinitrile of formula (4):



(4)

[where L^1 is as described above]
with a hydrazine R^3NHNH_2 or a salt thereof using the reagents and conditions described above for the preparation of compounds of formula (1) from alkenes of formula (2).

Intermediate dinitriles of formula (4) are either known compounds [see for example Tominaga, Y *et al ibid*; and Shioiri, T & Hamada, Y, J. Org. Chem. 43, 3631 (1978)] or may be prepared from known starting materials by methods analogous to those used for the preparation of the known compounds, for example as described in the Examples hereinafter. Thus, for example, in one general process malononitrile may be reacted with an appropriate acid $ArCO_2H$ or activated derivative thereof followed where necessary by generation of the leaving group L^1, for example by treating any $ArCOCH(CN)_2$ compound so obtained with trifluoromethanesulphonic anhydride in the presence of a base such as collidine to obtain the desired dinitrile $ArC(L^1)C(CN)_2$ where L^1 is a leaving group $-OSO_2CF_3$.

Where it is desired to obtain an intermediate of formula (3) wherein R^2 is other than a hydrogen atom this may be obtained by interconversion of the corresponding compound of formula (3) wherein R^2 is a hydrogen atom, by alkylation or acylation, as described hereinafter for the interconversion of compounds of formula (1).

Compounds of formula (1) may also be prepared by interconversion of other compounds of formula (1) and it is to be understood that the invention extends to such interconversion processes. Thus, for example, standard substitution approaches employing for example alkylation, arylation, acylation, thioacylation, sulphonylation, formylation or coupling reactions may be used to add new substitutents to and/or extend existing substituents in compounds of formula (1). Alternatively existing substituents in compounds of formula (1) may be modified by for example oxidation, reduction or cleavage reactions to yield other compounds of formula (1).

The following describes in general terms a number of approaches which can be employed to modify existing Ar, R^1, R^2, and R^3 groups in compounds of formula (1). It will be appreciated that each of these reactions will only be possible where one or more appropriate functional groups exist in the compound of formula (1).

Thus, for example alkylation or arylation of a compound of formula (1), for example to introduce a group Alk^1 or Ar^1 may be achieved by reaction of the compound with a reagent Alk^1L^2 or Ar^1L^2, where L^2 is a leaving group. This reaction is particularly suitable for alkylation or arylation of compounds of formula (1) where R^2 is a hydrogen atom.

Leaving groups represented by L^2 include halogen atoms such as iodine, chlorine or bromine atoms or sulphonyloxy groups such as alkyl- or arylsulphonyloxy groups, e.g. methylsulphonyloxy or p-toluenesulphonyl-oxy.

The alkylation or arylation reaction may be carried out in the presence of a base, e.g. an inorganic base such as a carbonate, e.g. caesium or

potassium carbonate, an alkoxide, e.g. potassium t-butoxide, or a hydride, e.g. sodium hydride, in a dipolar aprotic solvent such as an amide, e.g. a substituted amide such as dimethylformamide or an ether, e.g. a cyclic ether such as tetrahydrofuran, at around 0°C to around 40°C.

Alkylation as just described may also be used at low temperature in the preparation of a compound of formula (1) wherein R^1 is a methyl group from the corresponding compound of formula (1) in which R^1 is a hydrogen atom.

In another general example of an interconversion process, a compound of formula (1) may be acylated or thioacylated, for example to introduce a group $-C(O)Alk^1$ or $-C(S)Alk^1$. The reaction may be performed for example with an acyl or thioacyl halide or anhydride in the presence of a base, such as a tertiary amine e.g. triethylamine in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane at for example ambient temperature, or by reaction with a thioester in an inert solvent such as tetrahydrofuran at a low temperature such as around 0°C. The reaction is particularly suitable for use with compounds of formula (1) where R^2 is a hydrogen atom.

Compounds of formula (1) may be prepared in another general interconversion reaction by sulphonylation, for example by reaction of the compound with a reagent $R^6S(O)_nL^2$ where L^2 is a leaving group as described above in the presence of a base, for example an inorganic base such as sodium hydride in a solvent such as an amide, e.g. a substituted amide such as dimethylformamide at for example ambient temperature. The reaction may in particular be performed with compounds of formula (1) in which Ar and/or Ar^1 possesses a primary or secondary amino group.

In further examples of interconversion reactions according to the invention compounds of formula (1) may be prepared from other compounds of formula (1) by modification of existing functional groups in the latter.

Thus in one example, ester groups $-CO_2Alk^4$ in compounds of formula (1) may be converted to the corresponding acid [$-CO_2H$] by acid- or base-

catalysed hydrolysis depending on the nature of the group Alk^4. Acid- or base-catalysed hydrolysis may be achieved for example by treatment with an organic or inorganic acid, e.g. trifluoroacetic acid in an aqueous solvent or a mineral acid such as hydrochloric acid in a solvent such as dioxan or an alkali metal hydroxide, e.g. lithium hydroxide in an aqueous alcohol, e.g. aqueous methanol.

In a second example, $-OR^6$ [where Alk represents an alkyl group such as methyl group] groups in compounds of formula (1) may be cleaved to the corresponding alcohol -OH by reaction with boron tribromide in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane at a low temperature, e.g. around -78°C.

In another example, alcohol -OH groups in compounds of formula (1) may be converted to a corresponding $-OR^6$ group by coupling with a reagent R^6OH in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl-, diisopropyl-, or dimethylazodicarboxylate.

Aminosulphonylamino [$-NHSO_2NH_2$] groups in compounds of formula (1) may be obtained, in another example, by reaction of a corresponding amine [$-NH_2$] with sulphamide in the presence of an organic base such as pyridine at an elevated temperature, e.g. the reflux temperature.

In a further example, amine [$-NH_2$] groups in compounds of formula (1) may be obtained by hydrolysis from a corresponding imide by reaction with hydrazine in a solvent such as an alcohol, e.g. ethanol at ambient temperature.

In another example, a nitro [$-NO_2$] group may be reduced to an amine [$-NH_2$], for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an alcohol e.g. methanol, or by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

In a further example, amide [-CONHR^6] groups in compounds of formula (1) may be obtained by coupling a corresponding acid [-CO_2H] or an active derivative thereof, e.g. an acid anhydride, imide or halide, with an amine R^6NH_2. The coupling reaction may be performed using standard conditions for reactions of this type. Thus for example the reaction may be carried out in a solvent, for example an inert organic solvent such as an amide, e.g. a substituted amide such as dimethylformamide, at a low temperature, e.g. -30°C to ambient temperature, optionally in the presence of a base, e.g. an organic base such as a cyclic amine, e.g. N-methylmorpholine, and where necessary in the presence of a condensing agent, for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide.

N-oxides of compounds of formula (1) may be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C, or alternatively by reaction with a peracid such as peracetic acid in a solvent, e.g. dichloromethane, at ambient temperature.

The following Examples illustrate the invention.

All temperatures are in °C. The following abbreviations are used:
THF - tetrahydrofuran; DMF - dimethylformamide;
DMSO - dimethylsulphoxide

EXAMPLE 1

5-Amino-1-tert-butyl-3-(4'-chlorophenyl)pyrazole-4-carboxamide

To a solution of tert-butyl hydrazine hydrochloride (523 mg, 3.50 mmol) in ethyl alcohol (20 ml) was added powdered sodium hydroxide (168 mg, 4.20 mmol), followed by 3-(4-chlorophenyl)-2-cyano-3-methylthioacryl-amide (884 mg, 3.50 mmol) and the mixture was heated at reflux for 4h. On cooling, the solvent was removed under reduced pressure and the residue partitioned between water (80 ml) and ethyl acetate (80 ml). The aqueous layer was further extracted with ethyl acetate (2 x 80 ml) and the combined organic layers were washed with brine (1 x 100 ml), dried

($MgSO_4$) and concentrated under reduced pressure. The residue was subjected to column chromatography (SiO_2, 45-75% ethyl acetate-hexane) to afford the title compound (780 mg) after recrystallisation from methanol as a colourless solid m.p. 156°. δ_H (d^6 DMSO) 1.66 (9H, s), 5.16 (2H, br s), 5.68 (2H, br s), 7.42 (2H, dt, J 8.6, 2.1Hz), and 7.51 (2H, dt. J 8.7, 2.1Hz).

The acrylamide starting material was prepared according to the method of Y Tominaga *et al*, J. Het. Chem (1990), 27, 647-660 [see for example page 653 describing the preparation of compound 8h].

The following compound was prepared in a similar manner:

EXAMPLE 2

5-Amino-3-(4'-chlorophenyl)-1H-pyrazole-4-carboxamide

From 3-(4-chlorophenyl)-2-cyano-3-methylthioacrylamide (290 mg, 1 mmol) and hydrazine monohydrate (60 mg, 1.2 mmol) to give the title compound (60 mg) after recrystallisation from ethyl acetate as a colourless solid, m.p. 224°. δ_H (d^6 DMSO) Minor Tautomer 5.18 (2H br s), 6.25 (2H, br s), 7.52 (4H, m), 12.18 (1H, br s), Major Tautomer 5.95 (2H, br s), 6.25 (2H, br s), 7.52 (4H, m), and 11.92 (1H, br s).

EXAMPLE 3

5-Amino-1-tert-butyl-3-(4'-trifluoromethylphenyl)pyrazole-4-carboxamide

To a solution of 5-amino-1-tert-butyl-4-cyano-3-(4'-trifluoromethylphenyl)-pyrazole (308 mg, 1.0 mmol) in ethanol (15 ml) was added 10M sodium hydroxide (3 ml) and the mixture heated at reflux for 72h. On cooling, ethanol was removed under reduced pressure and water (50 ml) added. The resulting precipitate was collected by filtration, and washed with water (2 x 25 ml), to give the title compound (200 mg) as a colourless solid after recrystallisation from ethyl acetate m.p. 210-211°. δ_H ($CDCl_3$) 1.67 (9H, s), 5.16 (2H, br s), 5.69 (2H, br s), and 7.71 (4H, s).

The pyrazole starting material for this reaction was prepared as follows:

5-Amino-1-tert-butyl-4-cyano-3-(4'-trifluoromethylphenyl)pyrazole

To a solution of 2-(4-trifluoromethylbenzoyl)propanedinitrile (1.70 g, 7.15 mmol) in CH_2Cl_2 (60 ml), was added collidine (1.89 ml, 14.3 mmol)

followed by trifluoromethanesulphonic anhydride (1.45 ml, 8.58 mmol) and the mixture stirred at room temperature for 2h. The reaction was concentrated under reduced pressure and the residue dissolved in THF (100 ml). This was added to a suspension of tert-butyl hydrazine hydrochloride (0.98 g, 7.86 mmol) and sodium carbonate (1.14 g, 10.73 mmol) in THF and heated at reflux for 2.5h. The reaction was again concentrated under reduced pressure, the residue dissolved in ethyl acetate (100ml), washed with 2M hydrochloric acid (1 x 100 ml), water (1 x 100 ml) and brine (1 x 100 ml), dried ($MgSO_4$) and solvent then removed under reduced pressure. The resulting solid was subjected to column chromatography to give the title compound (700 mg) as a pale pink solid after recrystallisation from ether, m.p. 155-156°. δ_H ($CDCl_3$) 1.68 (9H, s), 4.46 (2H, br s), 7.66 (2H, d, J 8.0Hz), and 8.03 (2H, d, J 8.0Hz).

The dinitrile starting material for this reaction was prepared as follows:

2-(4-Trifluoromethylbenzoyl)propanedinitrile

To a solution of α, α', α"-trifluoro-p-toluic acid (4.56 g, 24.0 mmol) and malononitrile (1.45 g, 21.8 mmol) in DMF (50 ml) at 0° was added diethylcyanophosphonate (3.65 ml, 24.0 mmol) followed by triethylamine (9.40 ml, 69.8 mmol) and the mixture was stirred at 25° for 16h. The reaction was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (150 ml) and washed with 2 M hydrochloric acid (2 x 100 ml) and then with saturated $NaHCO_3$ (3 x 150 ml). The basic layers were acidified to pH 1 with 6M hydrochloric acid and extracted with ethyl acetate (3 x 125 ml). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give the title compound (1.90 g) as an orange solid which was not purified. δ_H ($CDCl_3$) 7.73 (4H, s), and 10.70 (1H, br s).

The following title compounds and intermediates of Examples 4-8 were prepared in a similar manner to the title compound and intermediates of Example 3.

EXAMPLE 4

5-Amino-1-tert-butyl-3-(3-furyl)pyrazole-4-carboxamide

From 5-amino-1-tert-butyl-4-cyano-3-(3-furyl)pyrazole (500 mg, 2.17 mmol) to give the title compound (340 mg) as a colourless solid m.p. 177°.

δ_H ($CDCl_3$) 1.65 (9H, s), 5.48 (2H, br s), 5.66 (2H, br s), 6.62 (1H, dd, J 1.8, 0.8Hz), 7.51 (1H, t, J 1.6Hz), and 7.68 (1H, dd, J 1.6, 0.9Hz).

The pyrazole starting material was obtained from 2-(3-furoyl)propanedinitrile as an orange solid m.p. 98-99°. δ_H ($CDCl_3$) 1.69 (9H, s), 6.83 (1H, dd, J 1.7, 0.8Hz), 7.44 (1H, t, J 1.7Hz) and 7.98 (1H, m). The 2-(3-furoyl)propanedinitrile was obtained from 3-furoic acid as an off-white solid. δ_H (d^6 DMSO) 6.77 (1H, dd, J 1.8, 0.8Hz), 7.70 (1H, t, J 1.7Hz), 8.14 (1H, dd, J 1.5, 0.8Hz), and 8.89 (1H, br s).

EXAMPLE 5

5-Amino-1-tert-butyl-3-(3-thienyl)pyrazole-4-carboxamide

From 5-amino-1-tert-butyl-4-cyano-3-(3-thienyl)pyrazole (492 mg, 2.0 mmol) to give the title compound (60 mg), as a colourless solid. m.p. 173-174° δ_H ($CDCl_3$) 1.71 (9H, s), 4.51 (2H, br s), 5.78 (2H, br s), 7.29 (1H, dd, J 4.9, 1.2Hz), 7.47 (1H, dd, J 4.9, 3.0Hz) and 7.60 (1H, m).

The pyrazole starting material was obtained from 2-(3-thienoyl)propanedinitrile as an off-white solid m.p. 132-133°. δ_H ($CDCl_3$) 1.67 (9H, s), 4.35 (2H, br s), 7.34 (1H, dd, J 5.0, 3.0Hz), 7.59 (1H, dd, J 5.0, 1.2Hz), and 7.84 (1H, dd, J 3.0, 1.3Hz). The 2-(3-thienoyl)propanedinitrile was obtained from 3-thiophenecarboxylic acid as a yellow solid m.p. 142-145° δ_H (d^6 DMSO) 6.86 (1H, br s), 7.38 (1H, dd, J 5.1, 1.3 Hz), 7.52 (1H, dd, J 5.1, 2.9Hz) and 7.99 (1H, dd, J 3.0, 1.3Hz).

EXAMPLE 6

5-Amino-1-tert-butyl-3-(4-tolyl)pyrazole-4-carboxamide

From 5-amino-1-tert-butyl-4-cyano-3-(4-tolyl)pyrazole (460 mg, 1.81 mmol) to give the title compound (128 mg) as a colourless solid, m.p. 240-242°. δ_H (d^6 DMSO) 1.55 (9H, s), 2.34 (3H, s), 6.26 (2H, s), 7.24 (2H, d, J 8.0Hz), and 7.33 (2H, d, J 8.0Hz).

The pyrazole starting material was obtained from 2-(4-toluoyl)propanedinitrile as a yellow solid m.p. 163°. δ_H ($CDCl_3$) 1.67 (9H, s), 2.36 (3H, s), 4.30 (2H, br s), 7.20 (2H, d, J 8.2Hz) and 7.80 (2H, d, J 8.2Hz). The 2-(4-toluoyl)propanedinitrile was obtained from p-toluic acid as an off-white solid m.p. >190° (decomp.). δ_H (d^6 DMSO) 2.35 (3H, s), 7.27 (2H, d, J 8.0Hz), 7.52 (2H, d, J 8.0Hz), and 10.82 (1H, br s).

EXAMPLE 7

5-Amino-1-tert-butyl-3-(3,4,5-trimethoxyphenyl)pyrazole-4-carboxamide

From 5-amino-1-tert-butyl-4-cyano-3-(3,4,5-trimethoxyphenyl)pyrazole (443 mg, 1.34 mmol) to give the title compound (30 mg) as a colourless solid m.p. 180-192°. δ_H (d^6 DMSO) 1.55 (9H, s), 3.69 (3H, s), 3.78 (6H, s), 6.29 (2H, br s), and 6.71 (2H, s).

The pyrazole starting material was obtained from 2-(3,4,5-trimethoxybenzoyl)propanedinitrile as an off-white solid m.p. 158-160°. δ_H (CD_3OD) 1.64 (9H, s), 3.79 (3H, s), 3.87 (6H, s), 4.80 (2H, s) and 7.14 (2H, s). The 2-(3,4,5-trimethoxybenzoyl)propanedinitrile was obtained from 3,4,5-trimethoxybenzoic acid as an off-white solid m.p. >140° (decomp). δ_H (d^6 DMSO) 3.69 (3H, s), 3.75 (6H, s), 3.95 (1H, br s), and 6.99 (2H, s).

EXAMPLE 8

From 5-amino-1-tert-butyl-4-cyano-3-(2-naphthyl)pyrazole (220 mg, 0.8 mmol) to give the title compound (44 mg) as a colourless solid m.p. 224-225°C. δ_H ($CDCl_3$) 1.69 (9H, s), 5.22 (2H, br s), 5.71 (2H, br s), 7.50-7.54 (2H, m), 7.65 (1H, dd, J 8.4, 1.6Hz), 7.80-7.93 (3H, m), and 8.04 (1H, s).

The pyrazole starting material was obtained from 2-(2-naphthoyl)-propanedinitrile as a colourless solid m.p. 121°. δ_H ($CDCl_3$) 1.71 (9H, s), 4.38 (2H, br s), 7.45-7.51 (2H, m), 7.81-7.93 (3H, m), 8.05 (1H, dd, J 8.6, 1.8Hz), and 8.41 (1H, s). The 2-(2-naphthoyl)propanedinitrile was obtained from 2-naphthoic acid as a yellow solid m.p. 195° (decomp.). δ_H ($CDCl_3$) 7.57-7.66 (2H, m), 7.71 (1H, dd, J 8.3, 1.7Hz), 7.89 (1H, d, J 7.6Hz), 7.94 (2H, d, J 8.3Hz), and 8.26 (1H. s).

EXAMPLE 9

5-Amino-1-phenyl-3-(4-tolyl)pyrazole-4-carboxamide

From 5-amino-4-cyano-1-phenyl-3-(4-tolyl)pyrazole (185 mg, 0.68 mmol) in a similar manner to the compound of Example 3 to give the title compound (29 mg) as a colourless solid m.p. 186-187° δ_H ($CDCl_3$) 2.41 (3H, s), 5.33 (2H, br s), 5.74 (2H, br s), 7.28 (2H, d, J 8.1Hz), 7.36-7.41 (1H, m), 7.48-7.53 (3H, m), 7.54 (1H, m), and 7.61 (2H, d, J 8.6Hz).

The pyrazole starting material for the above process was prepared as a colourless solid m.p. 169-170° δ_H ($CDCl_3$) 2.39 (3H, s), 4.64 (2H, br s), 7.16-7.32 (3H, m), 7.41-7.59 (4H, m), and 7.87 (2H, d, J 8.2Hz) from

phenylhydrazine and 2-(4-toluoyl)propanedinitrile in a similar manner to the intermediate pyrazole of Example 3.

EXAMPLE 10

5-Amino-1-tert-butyl-3-(4-methoxycarbonylphenyl)pyrazole-4-carboxamide

A mixture of 5-amino-1-tert-butyl-4-cyano-3-(4-methoxycarbonylphenyl)-pyrazole (448 mg, 1.5 mmol) and tetrakis(triphenylphosphine)ruthenium dihydride in dimethoxyethane (1 ml) and water (54 µl) was heated at 120° under a nitrogen atmosphere in a sealed tube for 18h. The reaction was concentrated under reduced pressure and the residue subjected to column chromatography (silica 4% methanol-CH_2Cl_2) to give the title compound (170 mg) after recrystallisation from ethyl acetate as a colourless solid m.p. 237-239°. δ_H ($CDCl_3$) 1.67 (9H, s), 4.39 (3H, s), 5.10 (2H, br s), 5.69 (2H, br s), 7.66 (2H, d, J 8.2Hz), and 8.11 (2H, d, J 8.3Hz).

The pyrazole starting material used in the above process was prepared as a light yellow solid m.p. 202-203°. δ_H ($CDCl_3$) 1.69 (9H, s), 3.93 (3H, s), 4.39 (2H, br s), 8.00 (2H, dt, J 7.6, 1.4Hz), and 8.08 (2H, dt, J 8.8, 2.0Hz) from 2-(4-methoxycarbonylbenzoyl)propanedinitrile in a similar manner to the intermediate pyrazole of Example 3.

The 2-(4-methoxycarbonylbenzoyl)propanedinitrile was obtained from monomethylterephthalate as an orange solid m.p. 153-160° (decomp.). δ_H (d^6 DMSO) 3.85 (3H, s), 6.62 (1H, br s), 7.65 (2H, dt, J 8.6, 1.9Hz), and 7.93 (2H, dt, J 8.6, 2.0Hz).

EXAMPLE 11

5-Amino-1-tert-butyl-3-phenylpyrazole-4-carboxamide

From 5-amino-1-tert-butyl-4-cyano-3-phenylpyrazole (720mg, 3.0mmol) in a similar manner to the compound of Example 3 to give the title compound as white crystals (92mg) m.p. 177-178°. δH ($CDCl_3$) 7.54 (2H, m), 7.45 (3H, m), 5.69 (2H, br s), 5.21 (2H, br s) and 1.67 (9H, s).

The pyrazole starting material for the above process was obtained as described for the intermediate pyrazole of Example 3 from 2-benzoyl-propanedinitrile as a white crystalline solid m.p. 124-125°. δH ($CDCl_3$) 7.93 (2H, m), 7.42 (3H, m) 4.37 (2H, br s) and 1.68 (9H, s). The 2-benzoylpropanedinitrile was prepared from benzoic acid following the

procedure described in Example 3 as a light yellow solid. δH ($CDCl_3$) 7.81 (2H, d, J 7.1Hz), 7.66 (1H, t, J 7.1Hz), 7.54 (2H, apparent t, J 7.1Hz) and 6.10 (1H, br s).

EXAMPLE 12

5-Amino-3-(4-tolyl)-1-(3-trifluoromethoxyphenyl)pyrazole-4-carboxamide

Powdered sodium hydroxide (88mg, 2.2mmol) was added to a solution of 3-trifluoromethoxyphenyl hydrazine hydrochloride (503mg, 2.2mmol) and 2-cyano-3-methylthio-3-(4-tolyl)acrylamide (464mg, 2.0mmol) in ethanol (20ml) and the mixture heated at reflux for 18h. On cooling, the solvent was removed under reduced pressure and the residue partitioned between water (80ml) and ethyl acetate (100ml). The aqueous layer was further extracted with ethyl acetate (2x80ml) and the combined organic layers washed with brine (100ml), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was recrystallised from isopropyl ether-heptane to give the title compound as white needles (320mg) m.p. 177-179°. δH ($CDCl_3$) 7.70 (1H, m), 7.51 (1H, d, J 8.0Hz), 7.38 (1H, d, J 8.0Hz), 7.40 (1H, m), 7.09 (1H, d, J 7.9 Hz), 5.74 (2H, br s), 5.35 (2H, br s) and 2.42 (9H, s).

The 2-cyano-3-methylthio-3-(4-tolyl)acrylamide starting material was prepared according to the method of Tominaga *et al* J. Het. Chem. (1990) 27, 647-660 to give the compound as white crystals m.p. 200-210°. δH ($CDCl_3$) 7.31 (2H, d, J 8.4Hz), 7.10 (2H, dt, J 8.4, 1.8Hz), 6.12 (1H, br s), 5.54 (1H, br s), 2.41 (3H, s) and 1.90 (3H, s).

EXAMPLE 13

5-Amino-1-(4-bromophenyl)-3-(4-tolyl)pyrazole-4-carboxamide

The title compound was prepared from 2-cyano-3-methylthio-3-(4-tolyl)acrylamide (928mg, 4.0mmol), 4-bromophenylhydrazine hydrochloride (894mg, 4.0mmol) and sodium hydroxide (176mg, 4.4mmol) following the procedure used for the compound of Example 12. The crude product was subjected to column chromatography (SiO_2, 10% methanol in CH_2Cl_2) and recrystallisation from ethyl acetate to give the title compound as white crystals (470mg) m.p. 222-223°. δH ($CDCl_3$) 7.63 (2H, dt, J 8.8,

2.2Hz), 7.52 (2H, dt, J 8.5, 2.6Hz), 7.48 (2H, d, J 7.4Hz), 7.28 (2H, d, J 8.3Hz), 5.74 (2H, br s), 5.29 (2H, br s), 2.41 (3H, s).

EXAMPLE 14

5-Amino-1-[(ethoxycarbonyl)methyl]-3-(4-tolyl)pyrazole-4-carboxamide

The title compound was prepared from 2-cyano-3-methylthio-3-(4-tolyl)acrylamide (425mg, 1.83mmol), ethyl hydrazinoacetate hydrochloride (311mg, 2.01mmol) and sodium hydroxide (80mg, 2.01mmol) following the procedure used for the compound of Example 12. The crude product was subjected to column chromatography (SiO_2, 10% methanol in CH_2Cl_2) and was recrystallised from ethyl acetate to give the title compound as white crystals (152mg) m.p. 179°. δH ($CDCl_3$) 7.43 (2H, d, J 8.1Hz), 7.26 (2H, d, J 8.1Hz), 5.56 (2H, br s), 5.22 (2H, br s), 4.77 (2H, s), 4.27 (2H, q, J 7.2Hz), 2.40 (3H, s) and 1.32 (3H, t, J 7.2Hz).

EXAMPLE 15

5-Amino-1-(2-pyridyl)-3-(4-tolyl)pyrazole-4-carboxamide

The title compound was prepared from 2-cyano-3-methylthio-3-(4-tolyl)acrylamide (4.64mg, 2.0mmol) and 2-hydrazinopyridine (218mg, 2.0mmol) following the procedure used for the compound of Example 12. The title compound was obtained as a white crystalline solid (350mg) m.p. 244-247°. δH (d^6DMSO) 8.46 (1H, dm, J 5.0Hz), 7.97 (1H, ddd, J 8.4, 7.4, 1.9Hz), 7.85 (1H, d, J 8.4Hz), 7.68 (2H, br s), 7.47 (2H, d, J 8.1Hz), 7.31 (2H, d, J 7.6Hz), 7.29 (1H, signal obscured by overlapping d), 3.30 (2H, s) and 2.37 (3H, s). MS (ES^+) 294 (MH^+, 100%).

EXAMPLE 16

5-Amino-1-(1-naphthyl)-3-(4-tolyl)pyrazole-4-carboxamide

The title compound was prepared from 2-cyano-3-methylthio-3-(4-tolyl) acrylamide (464mg, 2.0mmol), 1-naphthyl hydrazine hydrochloride (389mg, 2.0mmol) and sodium hydroxide (88mg, 2.2mmol) following the procedure used for the compound of Example 12. The crude product was subjected to column chromatography (SiO_2, 50-60% ethyl acetate in hexane) and was recrystallised from diethylether to give the title compound as pink crystals (185mg) m.p. 195°. δH ($CDCl_3$) 8.00 (1H, d, J

8.3Hz), 7.95 (1H., m), 7.73-7.55 (7H, m), 7.30 (2H, d, J 8.3Hz), 5.52 (2H, br s), 5.16 (2H, br s) and 2.42 (3H, s).

EXAMPLE 17

5-Amino-1-(2-tolyl)-3-(4-tolyl)pyrazole-4-carboxamide

The title compound was prepared from 2-cyano-3-methylthio-3-(4-tolyl) acrylamide (464mg, 2.0mmol), 2-tolylhydrazine hydrochloride (350mg, 2.2mmol) and sodium hydroxide (88mg, 2.2mmol) following the procedure used for the compound of Example 12. The crude product was subjected to column chromatography (SiO_2, 75% ethyl acetate in hexane) to give the title compound as a yellow solid (30mg) m.p. 133-135°. δH ($CDCl_3$) 7.52 (2H, d, J 8.1Hz), 7.38 (4H, m), 7.28 (2H, d, J 7.4Hz), 5.40 (4H, m), 2.40 (3H, s) and 2.23 (3H, s).

EXAMPLE 18

5-Amino-1-(4-methoxyphenyl)-3-(4-tolyl)pyrazole-4-carboxamide

The title compound was prepared from 2-cyano-3-methylthio-3-(4-tolyl) acrylamide (232mg, 1.0mmol), 4-methoxyphenylhydrazine hydrochloride (192mg, 1.1mmol) and sodium hydroxide (44mg, 1.1mmol) following the procedure used for the compound of Example 12. The crude product was purified by chromatography (SiO_2, 75% ethyl acetate in hexane) and recrystallisation from ethyl acetate-hexane to give the title compound as white crystals (101mg) m.p. 174-175°. δH (d^6DMSO) 7.49-7.43 (4H, m), 7.28 (2H, d, J 7.8Hz), 7.07 (2H, d, J 8.9Hz), 6.32 (2H, br s), 3.81 (3H, s) and 2.29 (3H, s), one set of amino protons not observed. MS (ES^+) 323 (MH^+, 100%).

EXAMPLE 19

5-Amino-1-(4-nitrophenyl)-3-(4-tolyl)pyrazole-4-carboxamide

The title compound was prepared from 2-cyano-3-methylthio-3-(4-tolyl)acetamide (464mg, 2.0mmol) and 4-nitrophenylhydrazine (337mg, 2.2mmol) following the procedure used for the compound of Example 12. The crude product was purified by column chromatography (SiO_2, 2% acetic acid, 5% methanol in CH_2Cl_2) to give the title compound as a yellow solid (14mg) m.p. 299-300°. δH (d^6DMSO) 8.42 (2H, d, J 8.6Hz), 8.21 (2H, d, J 8.7 Hz), 7.80 (2H, d, J 8.0Hz) and 7.75 (2H, d, J 7.9Hz).

EXAMPLE 20

5-Amino-1-(3-nitrophenyl)-3-(4-tolyl)pyrazole-4-carboxamide

The title compound was prepared from 2-cyano-3-methylthio-3-(4-tolyl)acrylamide (464mg, 2.0mmol), 3-nitrophenylhydrazine hydrochloride (417mg, 2.2mmol) and sodium hydroxide (88mg, 2.2mmol) following the procedure used for the compound of Example 12. The crude product was purified by column chromatography (SiO_2, 50% ethyl acetate in hexane) and recrystallisation from ethyl acetate to give the title compound as white crystals (50mg) m.p. 237-238°. δH (d^6DMSO) 8.42 (1H, s), 8.21 (1H, d, J 7.8Hz), 8.11 (1H, d, J 7.8Hz), 7.79 (1H, t, J 8.2Hz), 7.50 (2H, d, J 8.0Hz), 7.30 (2H, d, J 8.1Hz), 6.70 (2H, s), 5.50 (2H, br s) and 2.37 (3H, s).

EXAMPLE 21

5-Amino-1-(3-aminophenyl)-3-(4-tolyl)pyrazole-4-carboxamide

10% Palladium on carbon (100mg) was added to a de-gassed solution of the compound of Example 20 (120mg, 0.36mmol) and ammonium formate (30mg, 4.8mmol) in methanol. The reaction was stirred at room temperature and under nitrogen for 18h. The reaction mixture was filtered through a pad of Celite® and ethanol removed under reduced pressure. The residue was purified by column chromatography (SiO_2, ethyl acetate) to give the title compound (13mg) as yellow crystals after trituration with diethyl ether m.p. 220-222°. δH ($CDCl_3$) 7.45 (2H, d, J 8.0Hz), 7.30-7.20 (3H, m), 6.90 (1H, d, J 7.9Hz), 6.81 (1H, s), 6.62 (1H, d, J 8.0Hz), 5.41 (2H, br s), 2.63 (2H br s) and 2.39 (3H, s). MS (ES^+) 308 (MH^+, 100%).

EXAMPLE 22

5-Amino-1-(3-hydroxypropyl)-3-(4-tolyl)pyrazole-4-carboxamide

The title compound was prepared from 2-cyano-3-methylthio-3-(4-tolyl)acrylamide (464mg, 2.0mmol), sodium carbonate (424mg, 4.0mmol) and 1-(3-hydroxypropyl)hydrazinium trifluoroacetate (449mg, 2.2mmol) following the procedure used for the compound of Example 12. The crude product was subjected to column chromatography (SiO_2, 8% methanol in CH_2Cl_2) and was recrystallised from ethyl acetate to give the title compound as white crystals (240mg) m.p. 164-165°. δH ($CDCl_3$) 7.43 (2H, d, J 8.1Hz), 7.26 (2H, d, J 7.8Hz), 5.73 (2H, br s), 5.18 (2H, br s),

4.12 (2H, t, J 6.1Hz), 3.66 (2H, t, J 5.5Hz), 2.40 (3H, s), 2.04 (2H, quintet, J 6.1Hz) and 1.59 (1H, br s).

The hydrazine starting material was prepared following the method of A. Collet *et al* J. Org. Chem. 1993, 58, 4791-4793. A solution of N-(tert-butoxycarbonyl)-3-(4-cyanophenyl)-oxaziridine (1.03g, 4.2mmol) in anhydrous diethyl ether (10ml) was added to a solution of 3-amino-1-propanol (300mg, 4.0mmol) in diethyl ether (10ml) and the mixture stirred at room temperature for 2h. Solvent was removed under reduced pressure and the residue puified by chromatography (SiO_2, 3-5% methanol in CH_2Cl_2) to give 3-[1-(tert-butoxycarbonyl)hydrazino]-1-propanol as a white solid (400mg). δH ($CDCl_3$) 6.14 (1H, br s), 3.78 (2H, t, J 5.6Hz), 3.04 (2H, t, J 6.1Hz), 1.71 (2H, quintet, J 6.0Hz) and 1.46 (9H, s). MS (ES^+) 191 (MH^+, 100%). Treatment of this compound with trifluoroacetic acid gave the required 1-(3-hydroxypropyl)hydrazinium trifluoroacetate which was used without further purification.

EXAMPLE 23

5-Amino-1-[2-(1-hydroxy-2-methyl)propyl]-3-(4-tolyl)pyrazole-4-carboxamide

The title compound was prepared from 2-cyano-3-methylthio-3-(4-tolyl)acrylamide (418mg, 1.8mmol), sodium carbonate (424mg, 4.0mmol) and 1-[2-(1-hydroxy-2-methyl)propyl]hydrazinium trifluoroacetate (412mg, 2.0mmol) following the procedure used for the compound of Example 12. The crude product was subjected to column chromatography (SiO_2, 4% methanol in CH_2Cl_2) to give the title compound as a white solid (150mg) m.p. 219-220°. δH ($CDCl_3$) 7.43 (2H, d, J 7.8Hz), 7.26 (2H, d, J 7.8Hz), 5.78 (2H, br s), 5.22 (2H, br s), 4.22 (1H, t, J 7.1Hz), 3.88 (2H, d, J 6.6Hz), 2.40 (3H, s), and 1.58 (6H, s). MS (ES^+) 289 (MH^+, 100%).

The hydrazine starting material used in the above procedure was obtained from 2-amino-2-methyl-1-propanol (383mg, 4.3mmol) in a similar manner to the hydrazine prepared in Example 22. This gave 2-[2-(tert-butoxy-carbonyl)hydrazino]-2-methyl-1-propanol as a clear gum (400mg). δH ($CDCl_3$) 6.39 (1H, br s), 3.19 (2H, s), 1.42 (9H, s) and 0.97 (6H, s).

Treatment of this compound with trifluoracetic acid gave the required 1-[2-(1-hydroxy-2-methyl)propyl]hydrazinium trifluoroacetate which was used without further purification.

EXAMPLE 24

5-Amino-1-(3-carboxyphenyl)-3-(4-tolyl)pyrazole-4-carboxamide

The title compound was prepared from 2-cyano-3-methylthio-3-(4-tolyl)acrylamide (464mg, 2.0mmol), 3-carboxyphenylhydrazine (304mg, 2.0mmol) and triethylamine (2ml) following the procedure used for the compound of Example 12. The crude product was subjected to column chromatography (SiO_2, 2% acetic acid, 5% methanol in CH_2Cl_2) to give the title compound as a light yellow solid (340mg) m.p. 232-235°. δH (d^6DMSO) 8.14 (1H, s), 7.93 (1H, d, J 7.9Hz), 7.86 (1H, d, J 9.0Hz), 7.64 (1H, t, J 7.8Hz), 7.47 (2H, d, J 8.1Hz), 7.30 (2H, d, J 8.1Hz), 6.55 (1H, br s), 6.53 (1H, br s) and 2.36 (3H, s), carboxyl proton and amino protons not observed. MS (ES, +27V) 337 (MH^+, 100%);

EXAMPLE 25

5-Amino-1-(4-carboxyphenyl)-3-(4-tolyl)pyrazole-4-carboxamide

The title compound was prepared from 2-cyano-3-methylthio-3-(4-tolyl)-acrylamide (464mg, 2.0mmol) and 4-hydrazinobenzoic acid (334mg, 2.2mmol) following the procedure used for the compound of Example 12. The crude product was purified by column chromatography (SiO_2, 5-10% methanol +2% acetic acid in CH_2Cl_2) and by trituration with methanol to give the title compound as a light yellow solid (497mg) m.p. >310° dec. δH (d^6DMSO) 8.06 (2H, d, J 8.7Hz), 7.75 (2H, d, J 8.6Hz), 7.48 (2H, d, J 8.1Hz), 7.29 (2H, d, J 8.0Hz), 6.63 (2H, br s) and 2.36 (3H, s), carboxyl proton and amino protons not observed.

EXAMPLE 26

5-Amino-1-{3-[N-(N'-tert-butoxycarbonyl)-2-aminoethyl)]benzamido}-3-(4-tolyl)pyrazole-4-carboxamide

To a solution of the compound of Example 24 (150mg, 0.45mmol), N-hydroxysuccinimide (59mg, 0.51mmol), N-methylmorpholine (0.5ml, 4.50mmol) and N-(tert-butoxycarbonyl)ethylenediamine (82mg, 0.51mmol) in anhydrous DMF (15ml) was added 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (96mg, 0.51mmol) and the mixture stirred at room temperature for 20h. The reaction was partitioned between ethyl acetate (50ml) and water (50ml). The layers were separated and the

aqueous extracted with further portions of ethyl acetate (25ml x 2). The combined ethyl acetate extracts were washed with brine (50ml), dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow solid. The crude product was subjected to column chromatography (SiO_2, 4-5% methanol in CH_2Cl_2) to give the title compound as a white solid (100mg). δH (d^6DMSO) 8.57 (1H, t, J 6.9Hz), 8.03 (1H, s), 7.83 (1H, d, J 7.7Hz), 7.74 (1H, d, J 8.9Hz), 7.61 (1H, t, J 7.9Hz), 7.45 (2H, d, J 8.1Hz), 7.30 (2H, d, J 8.1Hz), 6.88 (1H, t, J 6.9Hz), 6.55 (2H, br s), 3.38 (2H, m), 3.10 (2H, q, J 6.0Hz), 2.36 (3H, s) and 1.35 (9H, s). MS (ES^+) 479 (MH^+, 100%).

EXAMPLE 27

5-Amino-1-[3-(N-{2-aminoethyl}benzamido)]-3-(4-tolyl)pyrazole-4-carboxamide trifluoroacetate

Trifluoroacetic acid (10ml) was added to a suspension of the compound of Example 26 (100mg, 0.21mmol) in CH_2Cl_2 (10ml). After 20 minutes the reaction mixture was concentrated under reduced pressure and the product triturated with diethyl ether to give the title compound as a buff powder (75mg). δH (d^6DMSO) 8.70 (1H, t, J 3.7Hz), 8.06 (1H, s), 7.87 (1H, d, J 7.3Hz), 7.78 (3H, m), 7.64 (1H, t, J 7.3Hz), 7.45 (2H, d, J 8.0Hz), 7.30 (2H, d, J 8.0Hz), 6.55 (2H, br s), 3.53 (2H, q, J 7.0Hz), 3.01 (2H, m) and 2.39 (3H, s). MS (ES^+) 379 (MH^+, 100%), 362 ($MH^+ - NH_3$, 45%).

EXAMPLE 28

5-Amino-1-{3-[N-(N'-(tert-butoxycarbonyl)-3-aminopropyl)]benzamido}-3-(4-tolyl)pyrazole-4-carboxamide

The title compound was prepared from the compound of Example 24 (215mg, 0.64mmol) and N-(tert-butoxycarbonyl)-1,3-diaminopropane (134mg, 0.77mmol) following the procedure used for the compound of Example 26. The crude product was purified by column chromatography (SiO_2, 5% methanol in CH_2Cl_2) to give the title compound as a white solid (80mg) m.p. 111-113°. δH (d^6DMSO) 8.55 (1H, t, J 6.2Hz), 8.03 (1H, s with fine coupling), 7.83 (1H, d, J 7.9Hz), 7.75 (1H, d, J 8.9Hz), 7.61 (1H, t, J 7.9Hz), 7.46 (2H, d, J 8.1Hz), 7.30 (2H, d, J 8.1Hz), 6.78 (1H, t, J 6.2Hz), 6.55 (2H, br s), 3.25 (2H, q, J 6.6Hz), 2.96 (2H, q, J 6.3Hz), 2.36 (3H, s), 1.63 (2H, quintet, J 6.9Hz), and 1.36 (9H, s).

EXAMPLE 29

5-Amino-1-[3-(N-{3-aminopropyl}benzamido)]-3-(4-tolyl)pyrazole-4-carboxamide trifluoroacetate

The title compound was prepared by treating the compound of Example 28 (80mg, 0.17mmol) with trifluoroacetic acid following the procedure used for the compound of Example 27. This gave the title compound as a white solid (86mg). δH ($CDCl_3$) 8.74 (1H, t, J 5.9Hz), 8.04 (1H, s), 7.85 (1H, d, J 7.8Hz), 7.79 (3H, m), 7.62 (1H, t, J 7.9Hz), 7.45 (2H, d, J 8.0Hz), 7.30 (2H, d, J 7.9Hz), 6.56 (2H, br s), 3.56 (2H, br s), 3.34 (2H, q, J 5.9Hz), 2.84 (2H, br s), 2.36 (3H, s) and 1.80 (2H, quintet, J 7.0Hz). MS (ES^+) 393 (MH^+, 100%).

EXAMPLE 30

5-Amino-1-{4-[N-(N'-(tert-butoxycarbonyl)-3-aminopropyl)]benzamido}-3-(4-tolyl)pyrazole-4-carboxamide

The title compound was prepared from the compound of Example 25 (160mg, 0.49mmol) and N-(tert-butoxycarbonyl)-1,3-diaminopropane (101mg, 0.58mmol) following the procedure used for the compound of Example 26. The crude product was purified by column chromatography (SiO_2, 5% methanol in CH_2Cl_2) to give the title compound as an orange solid (135mg) m.p. 109-110°. δH (d^6DMSO) 8.51 (1H, t, J 3.8Hz), 7.97 (2H, d, J 8.5Hz), 7.71 (2H, d, J 8.6Hz), 7.43 (2H, d, J 8.0Hz), 7.30 (2H, d, J 8.3Hz), 6.84 (1H, t, J 2.0Hz), 6.59 (2H, s), 3.28 (2H, m), 2.97 (2H, m), 2.36 (3H, s), 1.65 (1H, m) and 1.36 (9H, s). MS (ES^+) 493 (MH^+, 100%).

EXAMPLE 31

5-Amino-1-[4-(N-{3-aminopropyl})benzamido]-3-(4-tolyl)pyrazole-4-carboxamide trifluoroacetate

The title compound was prepared by treating the compound of Example 30 (110mg, 0.22mmol) with trifluoroacetic acid following the procedure used for the compound of Example 27. This gave the title compound as pale pink crystals (30mg) m.p. 118-120°. δH (d^6DMSO) 8.70 (1H, t, J 3.5Hz), 8.00 (2H, d, J 8.6Hz), 7.75 (2H, d, J 8.5Hz), 7.45 (2H, d, J 7.9Hz), 7.30 (2H, d, J 7.7Hz), 6.59 (1H, m), 3.35 (2H, m), 2.84 (2H, m), 2.36 (3H, s) and 1.81 (2H, m). MS (ES^+) 393 (MH^+, 100%).

BIOLOGICAL ACTIVITY

The following assays were used to demonstrate the activity and selectivity of compounds according to the invention. Enzymes for the assays were either obtained commercially or purified from known natural or recombinant sources using conventional methods.

$p56^{lck}$ kinase assay

The tyrosine kinase activity of $p56^{lck}$ was determined using a RR-src peptide (RRLIEDNEYTARG) and [γ-^{33}P]ATP as substrates. Quantitation of the ^{33}P-phosphorylated peptide formed by the action of $p56^{lck}$ was achieved using an adaption of the method of Geissler *et al* (J. Biol. Chem. (1990) 265, 22255-22261).

All assays were performed in 20mM HEPES pH 7.5 containing 10mM $MgCl_2$, 10mM $MnCl_2$, 0.05% Brij, 1μM ATP (0.5μCi[γ-^{33}P]ATP) and 0.8mg/ml RR-src. Inhibitors in dimethylsulphoxide (DMSO) were added such that the final concentration of DMSO did not exceed 1%, and enzyme such that the consumption of ATP was less than 10%. After incubation at 30°C for 15min, the reaction was terminated by the addition of one-third volume of stop reagent (0.25mM EDTA and 33mM ATP in dH_2O). A 15μl aliquot was removed, spotted onto a P-30 filtermat (Wallac, Milton Keynes, UK), and washed sequentially with 1% acetic acid and dH_2O to remove ATP. The bound ^{33}P-RR-src was quantitated by scintillation counting of the filtermat in a Betaplate scintillation counter (Wallac, Milton Keynes, UK) after addition of Meltilex scintillant (Wallac, Milton Keynes, UK).

The dpm obtained, being directly proportional to the amount of ^{33}P-RR-src produced by $p56^{lck}$, were used to determine the IC_{50} for each compound. The IC_{50} was defined as the concentration of compound required to reduce the production of ^{33}P-RR-src by 50%.

In this test, compounds according to the invention, such as the compounds of the Examples, have IC_{50} values of around 5μM and below.

Zap-70 and Csk kinase assays

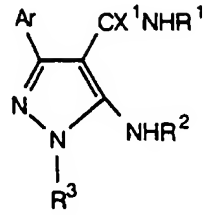
Inhibitor activity against Zap-70 or Csk kinase was determined using a capture assay based on that employed above for $p56^{lck}$ but with the following modifications. The RR-src peptide was replaced with polyGlu-Tyr (Sigma; Poole, UK) at a final concentration of 17 µg/ml. After addition of the stopped reaction to the filtermat, trichloroacetic acid 10% (w/v) was employed as the wash reagent instead of acetic acid and a final wash in absolute ethanol was also performed before scintillation counting. In these assays, compounds of the invention, such as the compounds of the Examples had little or no measurable activity against either Zap-70 or Csk kinases.

Protein kinase C assay

Inhibitor activity against protein kinase C (PKC) was determined using PKC obtained from Sigma Chemical Company (Poole, UK) and a commercially available assay system (Amersham International plc, Amersham, UK). Briefly, PKC catalyses the transfer of the γ-phosphate (^{32}p) of ATP to the threonine group on a peptide specific for PKC. Phosphonylated peptide is bound to phosphocellulose paper and subsequently quantified by scintillation counting. The inhibitor potency is expressed as either (i) the concentration required to inhibitor 50% of the enzyme activity (IC_{50}) or (ii) the percentage inhibition achieved by 10µM inhibitor. In this assay, compounds of the invention, such as the compounds of the Examples had little or no measurable activity at concentrations at which they inhibit the activity of $p56^{lck}$.

CLAIMS

1. A compound of formula (1):



(1)

wherein
Ar is an optionally substituted aromatic or heteroaromatic group;
X^1 is an oxygen or sulphur atom;
R^1 is a hydrogen atom or a methyl group;
R^2 is a hydrogen atom or a group $-Alk^1$ or $-X^2Alk^1$ where Alk^1 is an optionally substituted aliphatic or heteroaliphatic group and X^2 is a $-C(O)-$, $-C(S)-$, or $-S(O)_n$ group where n is an integer 1 or 2;
R^3 is a hydrogen atom or a group $-Alk^2$, [where Alk^2 is as defined for Alk^1], $-X^2Alk^2$, $-Ar^1$ [where Ar^1 is an optionally substituted aromatic or heteroaromatic group], $-Alk^2Ar^1$, or $-X^2Alk^2Ar^1$;
and the salts, solvates, hydrates and N-oxides thereof.

2. A compound according to Claim 1 wherein X^1 is an oxygen atom.

3. A compound according to Claim 1 or Claim 2 wherein R^1 and R^2 is each a hydrogen atom.

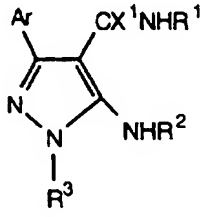
4. A compound according to any one of Claim 1 to Claim 3 wherein Ar is an optionally substituted phenyl group.

5. A compound according to any one of Claim 1 to Claim 4 wherein R^3 is an Alk^2, $-X^3Alk^2$, $-Ar^1$, $-Alk^2Ar$ or $-X^3Alk^2Ar^1$ group.

6. A compound according to Claim 5 wherein R^3 is an -Alk^2 or -Ar^1 group.

7. A compound according to Claim 6 wherein R^3 is an optionally substituted C_{1-6}alkyl, an optionally substituted phenyl or an optionally substituted pyridyl group.

8. A pharmaceutical composition comprising a compound of formula (1):



(1)

wherein
Ar is an optionally substituted aromatic or heteroaromatic group;
X^1 is an oxygen or sulphur atom;
R^1 is a hydrogen atom or a methyl group;
R^2 is a hydrogen atom or a group -Alk^1 or -X^2Alk^1 where Alk^1 is an optionally substituted aliphatic or heteroaliphatic group and X^2 is a -C(O)-, -C(S)-, or -$S(O)_n$ group where n is an integer 1 or 2;
R^3 is a hydrogen atom or a group -Alk^2, [where Alk^2 is as defined for Alk^1], -X^2Alk^2, -Ar^1 [where Ar^1 is an optionally substituted aromatic or heteroaromatic group], -Alk^2Ar^1, or -$X^2Alk^2Ar^1$;
and the salts, solvates, hydrates and N-oxides thereof.
together with one or more pharmaceutically acceptable carriers, excipients or diluents.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 97/01120

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D231/38 A61K31/415 C07D401/04 C07D405/04 C07D409/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1 285 932 A (CIBA-GEIGY AG) 16 August 1972 see page 6 - page 7; claims 1,18 ---	1-3,5-8
X	US 3 947 467 A (VERGE JOHN POMFRET ET AL) 30 March 1976 see column 11; example 2 ---	1-3,5-8
A	JOURNAL OF MEDICINAL CHEMISTRY, vol. 36, no. 4, 19 February 1993, WASHINGTON US, pages 425-432, XP000569376 T.R. BURKE JR. ET AL.: "Bicyclic Compounds as Ring-Constrained Inhibitors of Protein-Tyrosine Kinase p56lck1" see the whole document --- -/--	1-8

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
11 August 1997	22.08.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (- 31-70) 340-2040, Tx. 31 651 epo nl, Fax (- 31-70) 340-3016	Fink, D

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 97/01120

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Form PCT.ISA 210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

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PCT/GB 97/01120

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